UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,124	03/26/2001	Yasuo Nagasawa	4001-0001C	8886

7590 10/09/2003

SHANKS & HERBERT
TransPotomac Plaza
Suite 306
1033 N. Fairfax Street
Alexandria, VA 22314

EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,124	NAGASAWA ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,20 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,20 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

All objections and rejections not repeated in the instant Action have been withdrawn due to applicant's response to the previous Action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In the instant case, the application still lacks the required reference to the parent application of 09/308,164, and

the applicant failed to indicate why such a reference is not needed.

Claim Rejections - 35 USC § 103

Claims 12-13, 20, 30, 33, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stark et al (applicant reference AA) in view of Beach et al (U.S. Patent No. 6,025,192), for reasons of record set forth in the paper mailed 10/21/02 (and extended to new claims 30, 33, and 36 which are covered by the rejection). Applicants' arguments filed 4/8/03 have been fully considered but they are not deemed to be persuasive.

Response to Arguments

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Stark et al reference was not relied upon for a teaching of introducing a gene library and isolating a gene and thus the argument that the reference fails to teach the entire invention is not persuasive.

The applicant argues that Stark et al teach a method that is completely opposite of the goal of the present invention, focusing on identifying compounds which inhibit the activity of viral proteins instead of the present invention of locating a gene/protein that inhibits. The applicant indicates that further, Stark et al teaches away from the applicant's invention. This argument is not persuasive because genes and proteins are compounds too. In fact, the reference does teach assaying individual genes for inhibitory effects in the assay comprising introducing the genes into test cells (pages 44-46 of Stark et al). It is also noted by the reference that the mode of introduction (of the test compounds) will vary with the test compound. The teachings of Stark et al are not confined to non-protein/gene test compounds. What is not taught by the reference is the explicit use of a gene library as the test compounds and isolation of the gene after its identification in the assay as a functional test compound.

The applicant argues that the method of Stark et al is directed to the identification of compounds and is highly specialized for this singular goal and is not readily adapted for other purposes and that there is no suggestion of such modifications in the reference. This argument is not persuasive because genes and proteins are compounds that can be tested by

the assay of Stark et al as shown by the testing of specific genes/proteins at pages 44-46. The only adaptation necessary would be to use the appropriate method of introducing the test compounds which are genes/proteins expressed in a gene library into the assay. Stark et al teach to use the method of introduction would vary, and one of ordinary skill in the art (which skill is high) would find it obvious to use a transfection procedure to introduce the gene library into the cells taught by Stark et al (using a method such as that for the individual constructs of pages 44-46), hardly a difficult adaptation. The suggestion of the modifications comes from the teachings of Beach et al in combination with Stark et al which teaches the assaying of individual genes in the cell assays (pages 44-46).

The applicant argues that Stark et al focuses on finding compounds that inhibit the inhibition by an inhibitory substance, whereas, the present invention isolates genes and proteins that inhibit the transduction of specific intracellular signals that operate between a promoter region that responds to extracellular stimulation. This argument is not persuasive because, leaving aside the arguments drawn to gene library, addressed above, the difference that the applicant indicates exists is not claimed. The claims are merely drawn to cells

having a vectors holding a gene that induces cell death operably linked to a promoter region that functions in response to extracellular stimulation (which is under stimulation) and use of the surviving cells to isolate a gene from an introduced gene library. This is precisely what Stark et al teaches in the context of a broader method of screening test compounds. There are no claim limitations drawn to how the gene affects the claimed system, merely that the gene is isolated from surviving cells. A difference in systems, especially since the difference is not claimed, is not persuasive that the cited reference "teaches away from" the claimed invention because nothing in Stark et al teaches that some unclaimed alternative system would not be functional. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The applicant argues that Beach et al does not cure the deficiencies of Stark et al because the reference does not teach (the whole claimed invention) and the reference teaches methods that are completely different from the present invention. The applicant argues that the gene trapping method taught by Beach et al is only identifying genes that respond to a particular stimulus, not isolating a gene that inhibits specific

intracellular transduction signals that operates between a promoter and extracellular stimuli. This argument is not persuasive because Beach et al do teach introduction of a gene library into a cell which has a selectable marker expressed (like that as claimed) and assaying for the effect of the gene on the marker expression (like that as claimed), to identify and isolate the gene that affects the system. Because this reference also teaches that growth regulatory cytokines may be identified (or survival factors that suppress cell death) by expression of cDNA libraries directly in the target cells (the assay cells) (column 17, lines 39-41), this reference teaches that the gene library screening method taught by the reference is applicable to the type of system taught by Stark et al (which reads on the claimed system) and thus it would have been obvious to combine the teachings of the two references in order to identify and isolate genes as the test compounds that affect the Stark et al assay system. The applicant's arguments concerning what Beach et al fail to teach (and which it was not relied upon for the rejection) are nonpersuasive for the same reasons as that described above for Stark et al.

Therefore, in light of all of the available evidence, including the rejection set forth above and in the previous Office Action, the applicant's arguments and the arguments set

forth above, the claimed invention is still considered to have been obvious and the rejection of the claims under 35 USC 103 is maintained.

Claims 20 and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan et al (U.S. Patent No. 6,153,380) in view of Harant et al. This is a new rejection necessitated by the applicant's addition of new claims filed 4/8/03 which added new limitations to the claimed invention. Note: although claim 20 is included in the instant rejection, this is due to Patent Office policy in which base claims are included in the rejections of dependent claims.

Nolan et al teach a method of screening for a transdominant bioactive agent comprising the steps of introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, screening the plurality of cells for a cell exhibiting an altered phenotype, isolating the cell(s) exhibiting the altered phenotype, and isolating a candidate nucleic acid from the cell(s) (column 2). This reference teaches that the present invention provides methods and compositions to create, effectively introduce into cells, and screen compounds that affect a signaling pathway, also providing for the isolation of the constituents of the pathway (columns 2-3). The candidate

bioactive agents are taught as being the expression products of candidate nucleic acids (column 3). Nolan et al teach that "altered phenotype" is meant that the phenotype of the cell is altered in some way, preferably in some detectable and/or measurable way, such as cell viability or changes in expression of one or more proteins (column 21). Once a cell with an altered phenotype is detected, the cell is isolated from the plurality which do not have altered phenotypes by any number of ways as is known in the art including expression of a "survival" protein, expression of an enzyme that changes a non-fluorescent molecule to a fluorescent one, or overgrowth against a background of no or slow growth (columns 22-23). This reference teaches that the present methods are useful in inflammation application, including selection of agents which affect cytokine production or agents that bind cytokines such as TNF-alpha before they bind their receptor (columns 32-33). It is taught that IL-8 is among a number of pro-inflammatory cytokines (column 50). Cells containing reporter genes for detection of TNF-alpha and IL-1 promoter activity are taught: a TNF-alpha or IL-1 promoter region operably linked to a reporter gene such as luciferase, lacZ or GFP, used as a proxy measure of endogenous TNF-alpha and IL-1 promoter activity which will serve to allow for searches for peptides from their (nucleic acid) libraries

that act upon NF-kB or NFAT as well as unknown signaling pathways that are independent of NF-kB or NFAT critical to TNF-alpha and IL-1 signaling (column 52).

Nolan et al do not specifically teach use of the promoter of the IL-8 gene as the promoter that is extracellularly stimulated by TNF in the assay taught by the reference.

Harant et al teach that IL-8 is induced by IL-1 or TNF and that it involves particular parts of the IL-8 promoter (abstract). This reference teaches cells transfected with a plasmid comprising the interleukin-8 (IL-8) promoter fused to the coding region for luciferase (abstract). Nolan et al also teach stimulation of expression from the cells by contacting the cells with retinoids or TNF and assaying pro-inflammatory cytokines for stimulation of expression from the IL-8 promoter (page 26956, columns 1-2). This reference also teaches that NF-kB binding is essential for the transactivation by retinoids and TNF (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IL-1 promoter in the cells containing the IL-1 promoter operably linked to a reporter gene, and use the cells in assays to identify and isolate nucleic acids that affect the system as taught by Nolan et al because Nolan et al teach that it is

within the ordinary skill in the art to use a promoter operably linked to a reporter gene such as luciferase as a proxy measure of endogenous TNF-alpha or IL-1 promoter activity that will allow for searches for peptides from nucleic acid libraries that act upon NF-kB and that the assay methods taught are useful in inflammation application, including selection of agents which affect cytokine production or agents that bind cytokines such as TNF-alpha before they bind their receptor, specifically teaching that IL-8 is among a number of pro-inflammatory cytokines. Further, it would have been obvious to make the substitution because Harant et al teach that IL-8 is induced by IL-1 or TNF, involving part of the IL-8 promoter, and that NF-kB binding is essential to the activation, and Harant et al teach that it is within the ordinary skill in the art to use an IL-8 promoter operably linked to a reporter gene such as luciferase to assay pro-inflammatory cytokines for effects on expression or activity.

One would have been motivated to make the substitution for the expected benefit of identifying compounds and isolating constituents that affect the TNF/IL-8 signaling pathway because IL-8 is a pro-inflammatory cytokine, and thus would be useful for inflammation application, as taught by Nolan et al, using the IL-8 promoter-reporter constructs taught by Harant et al

which are useful in the assay because they are taught by the reference as responsive to TNF and pro-inflammatory cytokines. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 12-13, 20, and 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan et al and Harant et al as applied to claims 20 and 36-39 above, and further in view of Stark et al. This is a new rejection necessitated by the applicant's addition of new claims filed 4/8/03 which added new limitations to the claimed invention. Note: although claims 12-13 and 20 are included in the instant rejection, this is due to Patent Office policy in which base claims are included in the rejections of dependent claims.

Nolan et al and Harant et al were described above and applied as before.

Nolan et al and Harant et al together do not specifically teach operably linking the IL-8 promoter to a reporter gene that is capable of inducing cell death under specific conditions, such as a xanthine-guanine-phosphoribosyltransferase gene and

using cells that are HGPRT deficient in the assays made obvious by the references.

Stark et al teach cell lines transfected with constructs (vectors) which express a reporter compound under the control of a regulatory region (such as an interferon-inducible regulatory region) inducible directly or indirectly by a stimulating substance (which causes cytokine production or utilization). This reference teaches that the reporter compound can be luciferase, CAT, beta-glucuronidase, or a number of other genes for which detection systems are available or cytotoxic and expression of the compound is indicated by the death of the cells, such as HGPRT when 6-thioguanine is used in a HPRT- cell line. Stark et al teach a method of using the cell lines transfected with the constructs comprising exposing the cells to a test compound, stimulating the reporter gene construct under the control of the regulatory region and testing whether the cells die or not (for cytotoxic reporters) or detecting the activity of the reporter (for non-cytotoxic reporters).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the reporter gene, used in the assay methods made obvious by the combined teachings of Nolan et al and Harant et al, with the xanthine-guanine-phosphoribosyltransferase gene and use the

constructs in HGPRT deficient cells as taught by Stark et al because Stark et al teach that it is within the ordinary skill in the art to use any number of other genes for which detection systems are available or cytotoxic and expression of the compound is indicated by the death of the cells, such as HGPRT, in assays measuring expression from an inducible promoter such as an interferon-inducible regulatory region and Nolan et al teach that the assays taught by the reference can screen for an altered phenotype of the cell, preferably in some detectable and/or measurable way, such as cell viability or overgrowth against a background of no or slow growth.

One would have been motivated to do so for the expected benefit of using a desirable alternative reporter system taught by Stark et al in the assays made obvious from the combined teachings of Nolan et al and Harant et al, which alternative system is of a type that is taught by Nolan et al as being a good alternative in the assays taught by Nolan et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

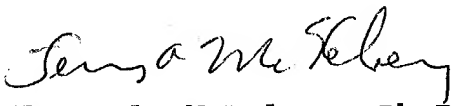
Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone

number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

October 8, 2003